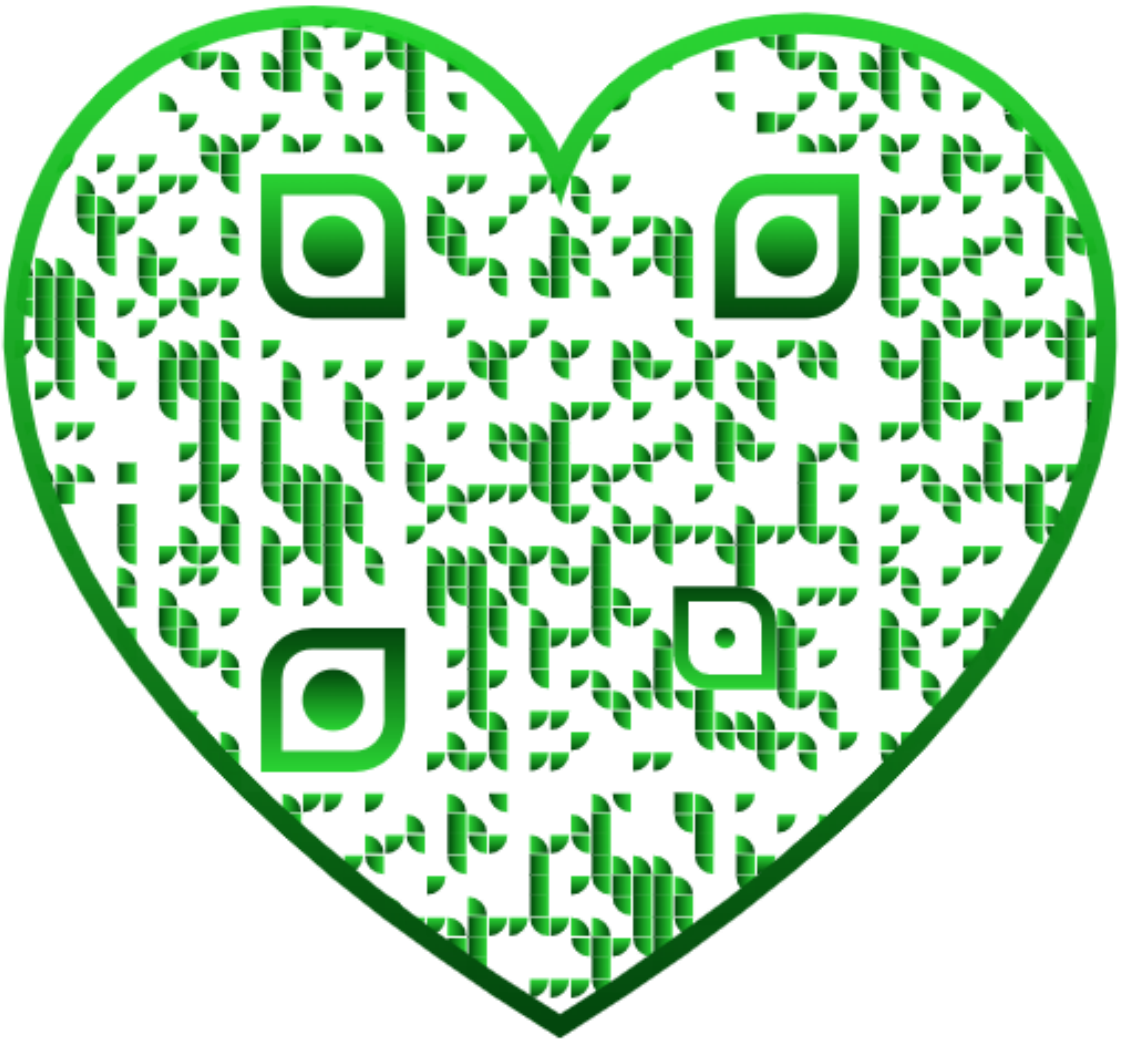
2020

PHYSIOLOGY
FIRST YEAR

Nerve

Dr/ NAGEEB



Introduction

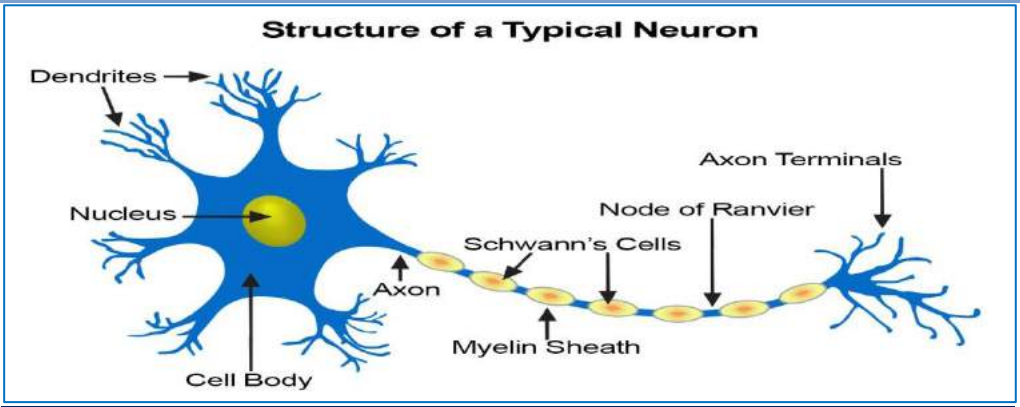
Structure of neuron:

A. The cell body (soma):

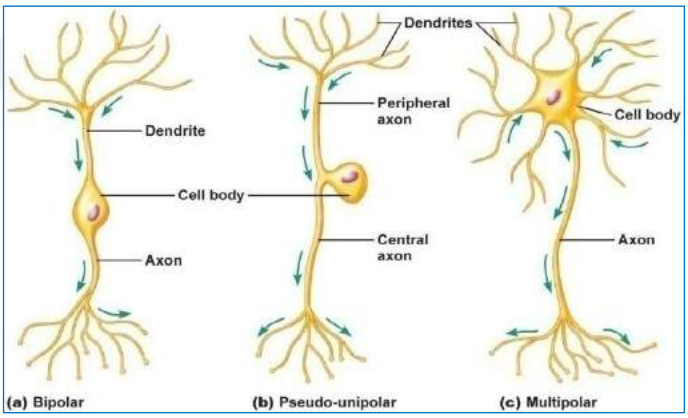
- ❑ No centeriole. So, the nerve cell can't divide.
- ❑ Rich mRNA.
- ❑ Nissile granules (for protein synthesis).

B. The cell processes: 2 types of processes:

Dendrites	Axon
Carry impulse **to** cell body.	Carry impulse **away** from cell body.
Multiple & Short	Single & Long Arise from *axon hillock* (most excitable part).



Types of neuron:



A. According to the processes: (shape)

1) **Unipolar:**
2) **Bipolar:**
3) **Multipolar:**

B. According to function:

1) **Sensory** (Afferent) which → carry **sensations** from organs → to the CNS.
2) **Motor** (Efferent) which → arise from CNS to carry **orders** → to organs.

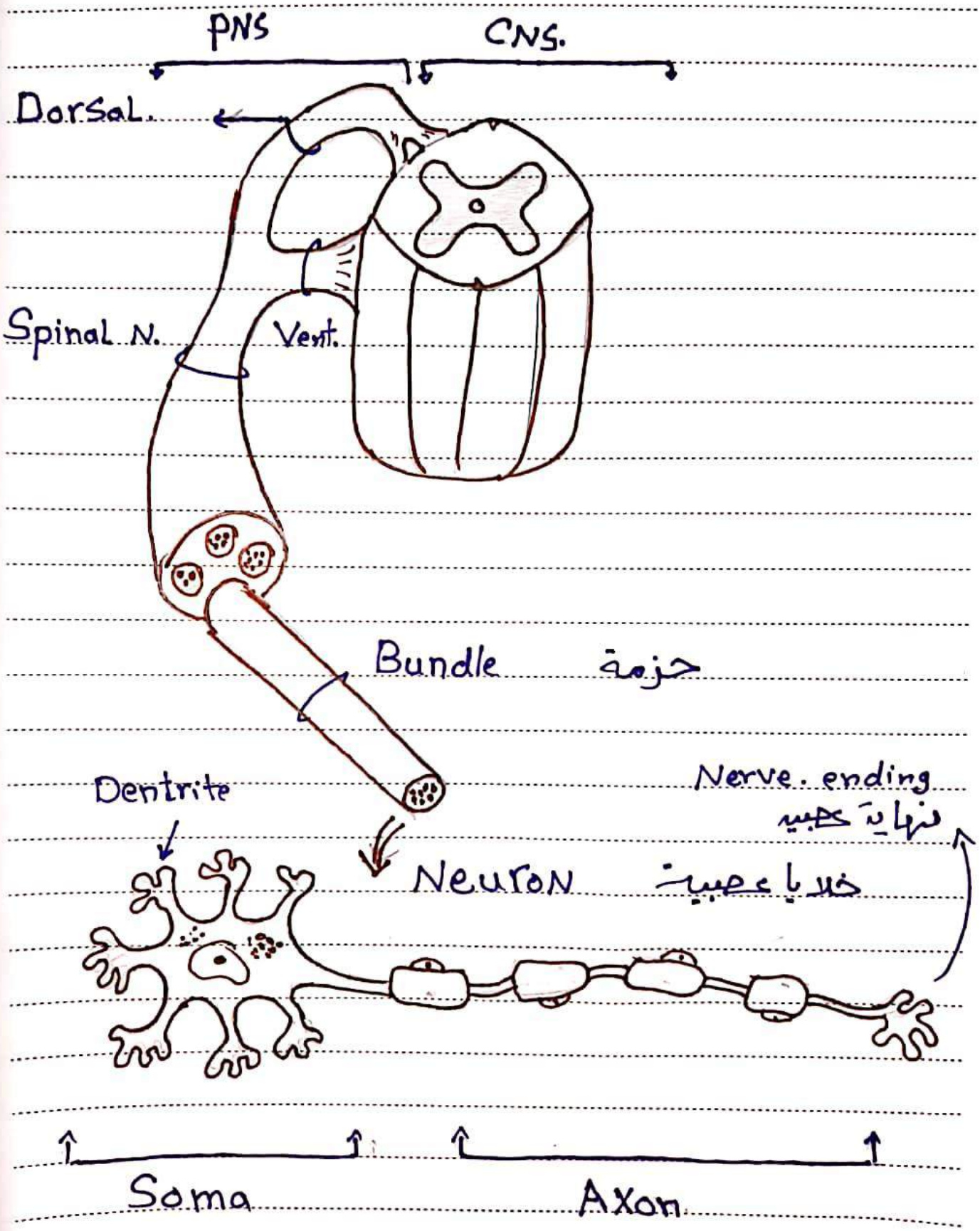
C. According to myelination:

1) **Myelinated** nerve fiber: e.g. preganglionic neuron.
2) **Non-myelinated** nerve fiber: e.g. postganglionic neuron.

D. According to diameter:

A & **B** & **C** (See later).

تعاظمني ذنبي فلّما قرنتهُ بعفوكَ ربي كانَ عفوكَ أعظما

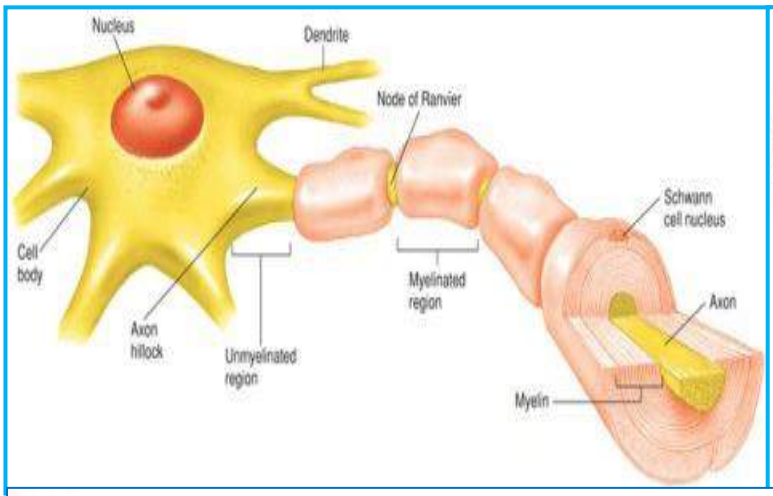

PNS
CNS.
Dorsal.
Spinal N.
Vent.
Bundle
حزمة
Dentrite
Nerve. ending
نهاية عصبية
Neuron
خلايا عصبية
Soma
Axon

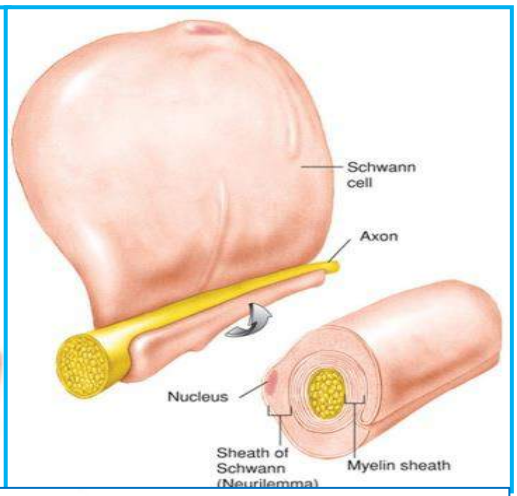
The myelin sheath:

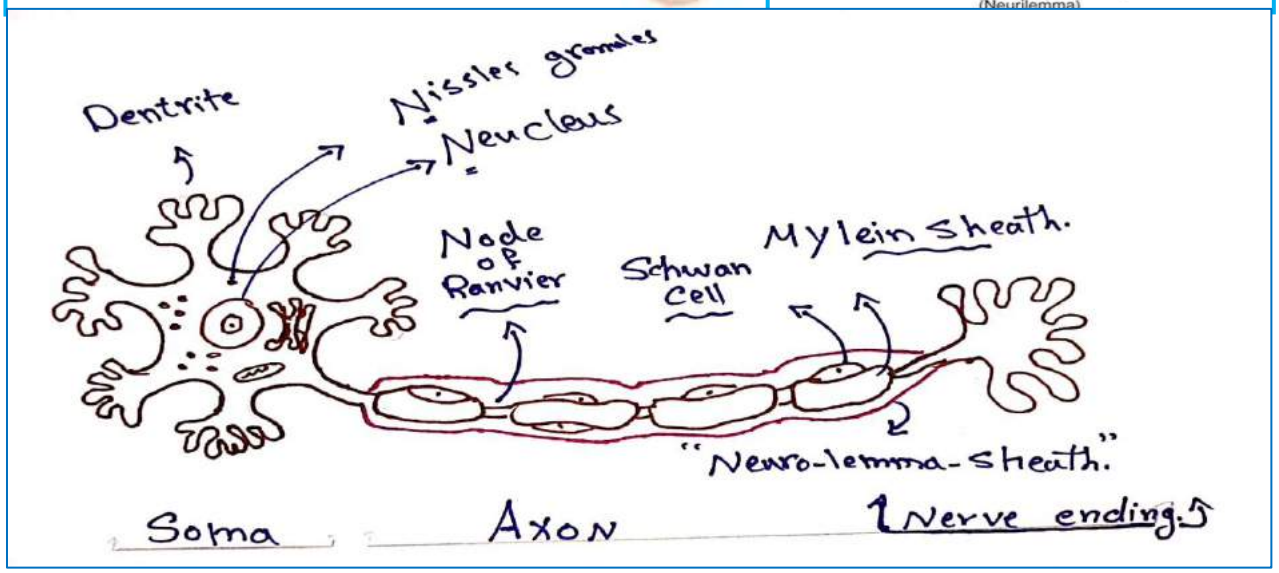
- It is a thick layer around the axon formed of **lipoprotein** substance.
- It is covered by outer neuro-lemmal sheeth , and interrupted by nodes of Ranvier, through which ions can pass.

Function ?

- It is insulator to electric currents.
- So, increase speed of conduction.
- Formed by the **Schwann cell** which rotates around the axon many times forming multiple layers.
- **In CNS**, the myelin sheath is formed by **oligodendroglia** cells.





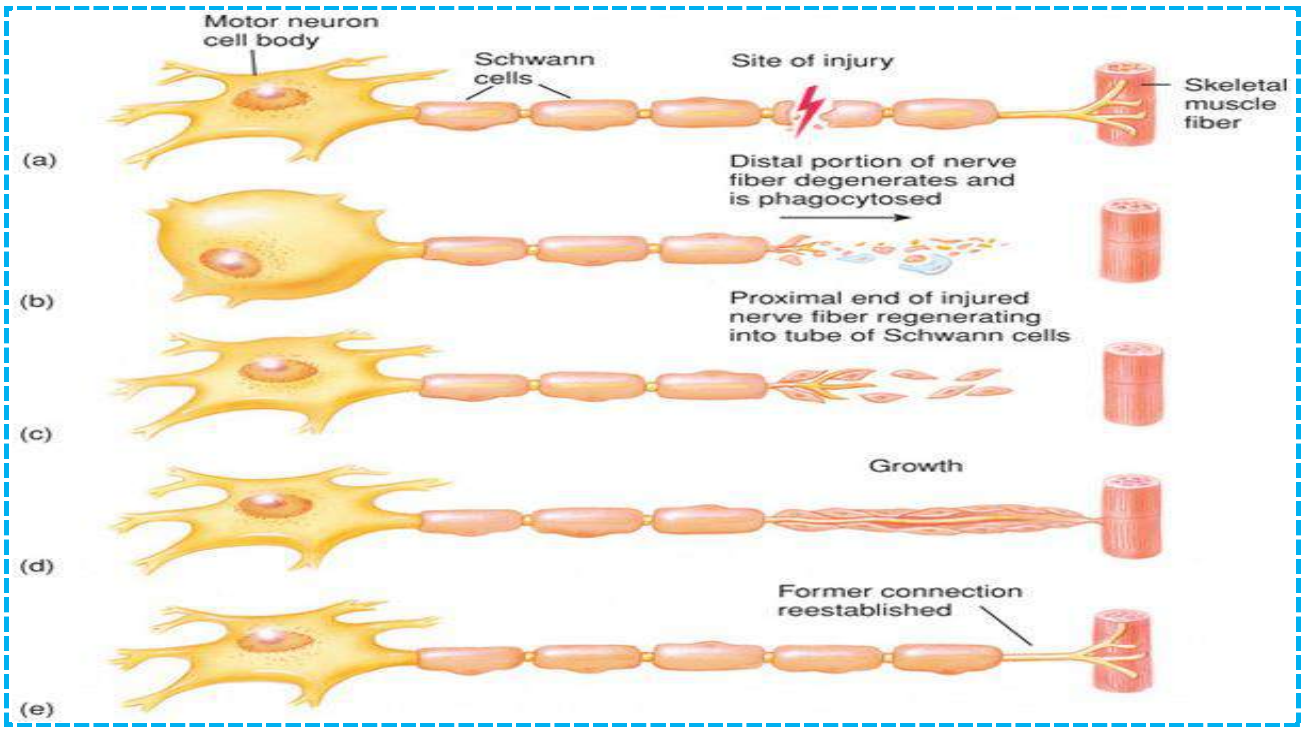


بينما أنت مُنهمكٌ في البُعد عن الله، يخلقُ الله موقفًا عصيبًا يُعيد إليك توازنك، بخُذلان قريب رُبما .أو بوعكة جسد لتضيق بك المساحات ذرعًا وتجد عند الله الخَلاص والمُتسّع

Degeneration & Regeneration of nerve fiber

- If the axon is cut, the part distal to cut degenerates (**Wallerian degeneration**) and the cell body degenerates (**Retrograde degeneration**).
- Then, (**Regeneration**) occurs.

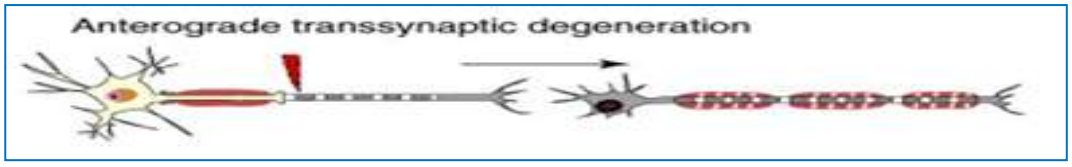
Wallerian degeneration:	Retrograde degeneration:
It occurs in the **1- *distal fragment.*** **2- *The proximal part of axon*** It starts 3 – 4 days after cutting.	It occurs in the ***soma " proximal ".***
The ***axon*** swells and ***breaks*** into short parts. The ***myelin*** sheath ***breaks*** into oily droplets.	The ***cell swells***
(due to osmosis of water by increase intracellular Na+ due to inhibition of Na+ - K+ pump)	
Then ***macrophages*** clean the area by the removal of the fragments.	Nissile granules disappear (***chromatolysis***), Golgi apparatus disappears
The Schwann cells divide forming ➔ cords of cells. … So, finally we get an empty ***neuro-lemmal tube.***	The nucleus is ***displaced to the periphery*** and may be extruded → causing death of the cell.



إذا المَرءُ لا يَرعاكَ إلاّ تَكَلُّفاً.... فَدَعهُ وَلا تُكثِر عَلَيهِ التَأَسُّفا

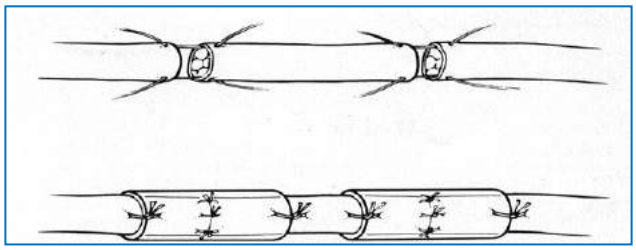
1. Transneural degeneration:

- In rare cases, degeneration of **pre**ganglionic neuron may lead to degeneration of the **post**ganglionic neuron. Specially if there is **no** convergence.



Regeneration

- Repair of the cell body starts about **20 days** after cutting and complete in **80 days**. (if the condition is **suitable**).
- The **Nissile** granules and **Golgi** apparatus reappear.
- The **nucleus** returns central and the **cell body** returns to its size.
- The **axon** grow at rate of **1 – 4 mm/day** (and at the gap **0.25 mm/day**).
- If the **gap** between the two cut ends is more than **3 mm**, regeneration fails except if the two ends are approximated by:
  a) Suturing the cut ends.
  b) Nerve graft



Cross regeneration:

- It is the growth of the axon of one neuron into the empty neuro-lemmal tube of another neuron.
- This is treated by **re-habilitation**.
-

Synapse

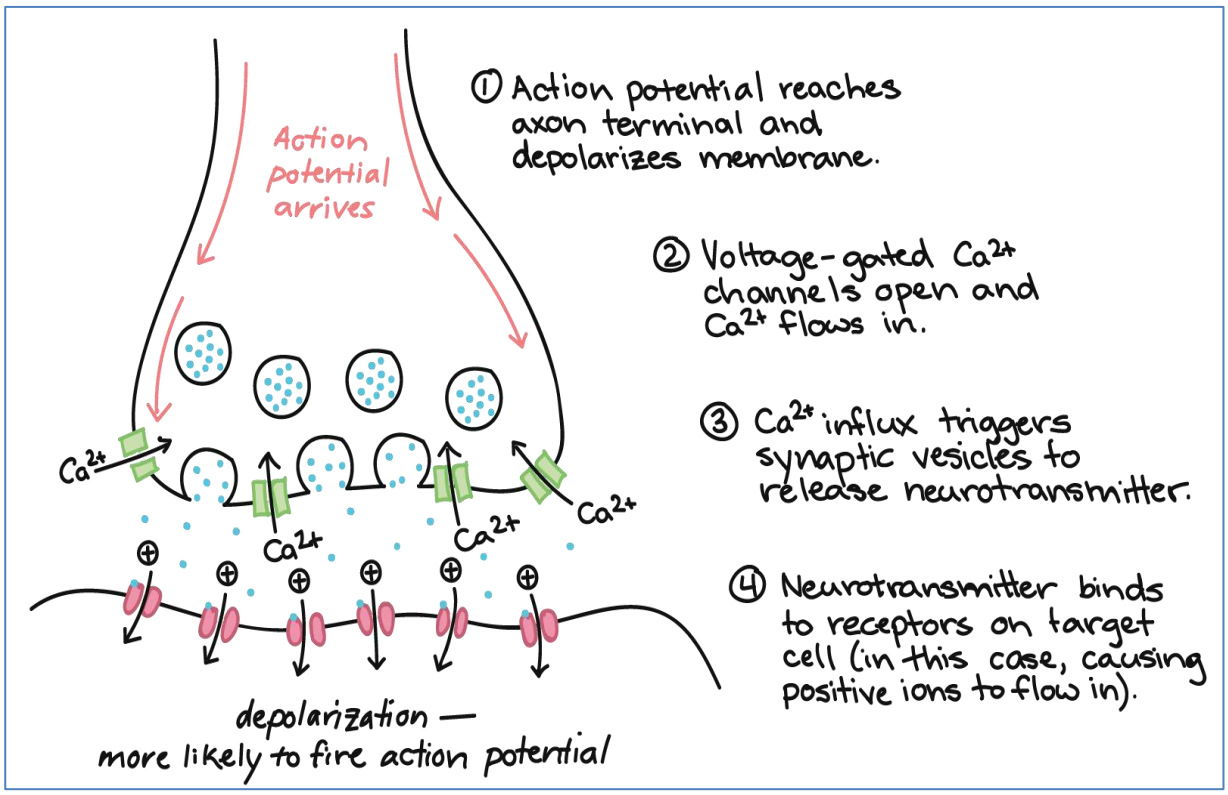
Definition: It is the junctional area between

- two neurons / or
- a neuron and organ

Structure:

- The neuron that transmits impulses ***towards*** the synapse is called ***presynaptic neuron***
- the neuron that transmits impulses ***away*** from the synapse is called ***postsynaptic neuron***
- the cell membrane of the presynaptic is called the ***pre-synaptic membrane***
- the cell membrane of the postsynaptic is called the ***post-synaptic membrane***.
- It is a cleft, 30-50 nm wide, separates the nerve ending from the next cell .

- ***Type of neural synapse may be:***
  a) **Axo – Deneretic** synapse (**most common**).
  b) **Axo – Somatic** synapse.
  c) **Axo – Axonic** synapse (**most rare**, but **most excitable because axon hillock are rich in Na channel with great response**).


Action potential arrives
① Action potential reaches axon terminal and depolarizes membrane.
② Voltage-gated Ca2+ channels open and Ca2+ flows in.
③ Ca2+ influx triggers synaptic vesicles to release neurotransmitter.
④ Neurotransmitter binds to receptors on target cell (in this case, causing positive ions to flow in).
Ca2+
depolarization — more likely to fire action potential

Transmission of impulses across synapses by :

Pre-synaptic release ***chemical transmitter*** in synaptic cleft → which acts on **receptors** on post-synaptic membrane → causing its **depolarization**.

The Mechanism Of Transmitter Release At The Synapse:

- the presynaptic nerve ending shows a swelling called the ***synaptic knob.*** **Ok baby ?**
- The chemical transmitter is stored in the synaptic knob in small vesicles called → ***synaptic vesicles*** when the **action potential** reaches the synaptic knob → The **voltage-gated Ca2+ channels** are opened allowing **Ca2+** influx into the cytoplasm → **Ca binds with the synaptic vesicles**.

➔ The vesicles get attached to specific "**release sites**" at the presynaptic membrane → then rupture and the chemical transmitter is released in the **synaptic cleft.**

➔ The chemical transmitter moves by simple diffusion to the receptors on the postsynaptic membrane → activates them → **A postsynaptic potential** is then generated in the postsynaptic membrane

TYPES OF SYNAPTIC POTENTIALS

1- Excitatory synaptic potentials:	2- Inhibitory synaptic potentials:
1) Excitatory post synaptic potential (EPSP): - EPSP occurs by release of **excitatory** transmitter (as **Ach**). - This cause **depolarization** in **POST**synaptic membrane. - Mechanisms of depolarization: **1.** Opening of Na^+ channels ⇨ ⇧ Na^+ influx. **2.** Closure of K^+ channels ⇨ ⇩ K^+ outflux. **3.** Closure of Cl^- channels ⇨ ⇩ Cl^- influx.	**1) Inhibitory post synaptic potential (IPSP): (Direct Inhibition):** - IPSP occurs by release of **inhibitory** transmitter (as **GABA**). - This cause **hyperpolarization** in **POST**synaptic membrane. - Mechanisms of hyperpolarization: **1.** Closure of Na^+ channels ⇨ ⇩ Na^+ influx. **2.** Opening of K^+ channels ⇨ ⇧ K^+ outflux. **3.** Opening of Cl^- channels ⇨ ⇧ Cl^- influx.

Synaptic summation:

Baby .. ? EPSP cannot alone depolarize the whole postsynaptic membrane.

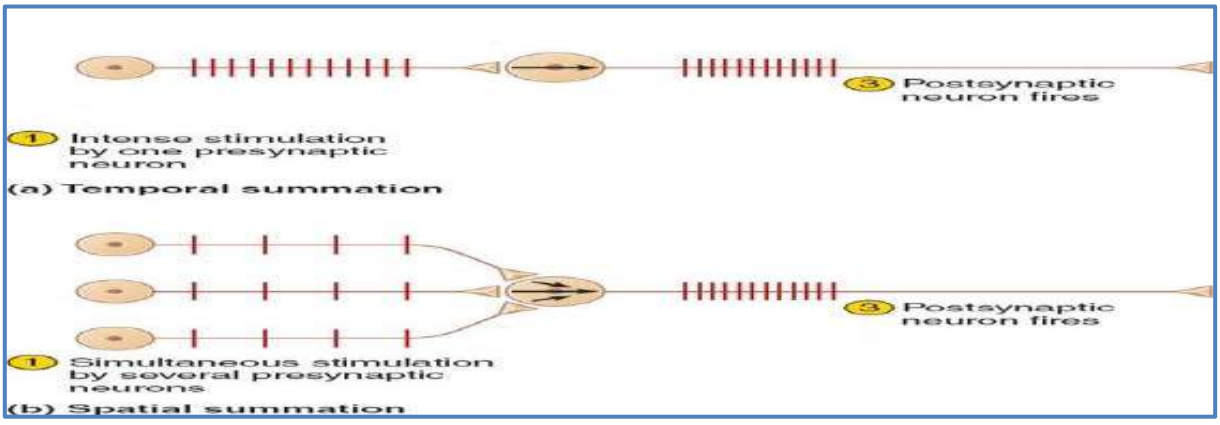
So, summation must occurs to reach firing level by two mechanism :

1- Temporal summation:

Repetitive stimulation of one presynaptic fiber by Train of impulses & **Time between stimuli less** than time of EPSP.

2- Spatial summation:

Stimulation of **Several** presynaptic fibers at the **Same time.**


Postsynaptic neuron fires
1 Intense stimulation by one presynaptic neuron
(a) Temporal summation
Postsynaptic neuron fires
1 Simultaneous stimulation by several presynaptic neurons
(b) Spatial summation

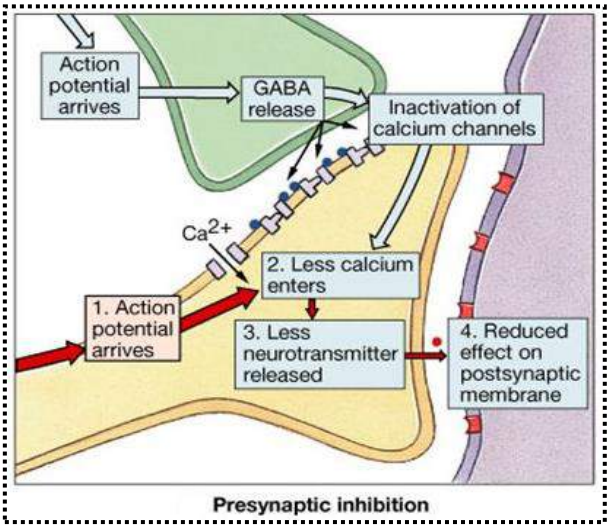
3- Presynaptic inhibition: (Indirect Inhibition):

In which interneurons synapse with **PREsynaptic** membrane shortly before the synapse and release **GABA** at → **the PREsynaptic membrane**.

GABA ⇨ inhibition of release of chemical transmitter from **PREsynaptic** membrane by one of the following:

1- **Closure** of Ca++ channels in presynaptic membrane ⇨ ⇩ Ca++ influx ⇨ ⇩ release of excitatory transmitter ⇨ ⇩ stimulation of postsynaptic membrane

2- **Hyperpolarization** in PREsynaptic membrane by Opening of Cl- channels ⇨ ⇧ Cl- influx.



Presynaptic inhibition

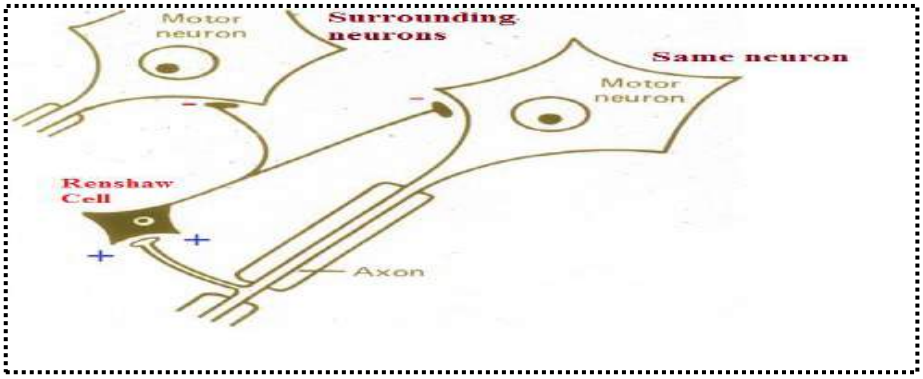
4- Negative feedback inhibition

(Lateral Inhibition):

- It occurs specially in spinal cord due to presence of **Renshaw cells.**
- When AHC receives excitatory impulses from the higher centers → it stimulates the surrounding Renshaw cells.

Renshaw cells in turn inhibit:

- ✓ The Same activated AHCs why ? **to prevent prolonged excitation**.
- ✓ The Surrounding AHCs .. why ? **to localize the action**.



سَلامٌ عَلى الدُنيا إذا لَم يَكُن بِها ... صَديقٌ صَدوقٌ صادِقُ الوَعدِ مُنصِفا

Properties of synaptic transmission

1. UniDirectional:

- Impulses are transmitted in one direction from pre to postsynaptic neuron.
  Why ? Because presynaptic neuron contain transmitter & post contain receptors.

2. Synaptic Delay:

- It is the time between arrival of the impulse to the synaptic knob and the excitation of the postsynaptic membrane.
- The minimal time for the synaptic delay = **0.5 msec**.
- The synaptic delay is caused by:
  1) Release of transmitter and diffusion through synaptic cleft to combine with its specific receptors.
  2) Na^+ influx to produce the (EPSP).
  3) Summation of many EPSPs to reach firing level.

Total reflex time:

- It is the time between the application of the stimulus and the appearance of the response.

Central delay:

- It is the total time needed for all synapses. (inside CNS).
  Central delay = total reflex time – (conduction in aff. & eff. + LP of muscle).
  It is also called (reduced reflex time).

Number of synapses:

- Can be calculated for any reflex:
  Number of synapses = Central delay / Synaptic delay.

	Facilitation (Potentiation)	Fatigue:
Definition	▪ **Slow** repeated synaptic stimulation ⇨ ⇧ EPSP ⇨ This may last from few second to even many hours. ▪ Facilitation explains memory or learning.	▪ **Rapid** repeated stimulation of presynaptic neuron ⇨ ⇩ **discharge** from the postsynaptic neurons. ▪ Fatigue explains passive theory of sleep.
Mechanism	Accumulation of Ca+2 in presynaptic neuron	Due to depletion of chemical transmitter in synaptic knobs

5. Factors affecting synaptic transmission:

- Synaptic transmission is affected by some chemical & biological factors:

Factors ⇧ synaptic transmission	Factors ⇩ synaptic transmission
Alkalosis: pH 7.8 ⇨ convulsion. As in: epilepsy.	**Acidosis:** pH 7 ⇨ coma. As in: diabetic keto-acidosis & renal failure
Caffeine: By increase excitability **Strychnine:** By inhibition of the inhibitory chemical transmitter (GABA). **Some bacterial toxins as tetanus:** By inhibition of the inhibitory chemical transmitter (GABA) ⇨ ⇧ Ach. ⇨ uncontrollable fatal muscle spasm.	**Sedative & Hypnotic & Anesthetic:** By: ⇩ Amount of excitatory transmitters. ⇧ Amount of inhibitory transmitters. **Hypoxia:** Causes loss of consciousness within 3-5 seconds. **Hypoglycemia:** Has the same effect.

Excitability of nerve

🕮 Definition:

- It is the ability of the living tissue to **respond** to an **adequate stimulus**.

🕮 The stimulus:

- It is the **change** in the environment of the living tissue which may be electrical, chemical, mechanical or thermal.
- However the electrical stimuli are commonly used in the form of:
    1) **Galvanic current:** **L**ow intensity & **L**ong duration = direct. (DC).
    2) **Faradic current:** high intensity & short duration = alternative. (AC).

Factors determine the effectiveness of the stimulus

1. Intensity (strength) of the stimulus:

- **Threshold stimulus:** it is the minimal intensity which produce impulse
- **Sub-threshold stimulus:** ⇨ no impulse (but local response).
- **Supra-threshold stimulus:** ⇨ the same impulse of the threshold. But, in less time.

The single nerve fiber obeys all or none law.
(When nerve is stimulated, it either gives a response or no response at all
Minimal stimulus give maximal response ,and increase the intensity of stimulus above level of threshold produce no further increase in action potential as long as factor affect excitability are constant).
The tissues that obey the all or none law are:

- Single nerve fiber.
- Motor unit of skeletal muscle and Single muscle fiber
- smooth muscle.
- Cardiac muscle

2. Duration of the stimulus:

- ⇧ Intensity of stimulus ⇨ ⇩ Duration needed to give response.
- This is studied in the **strength-duration curve**.

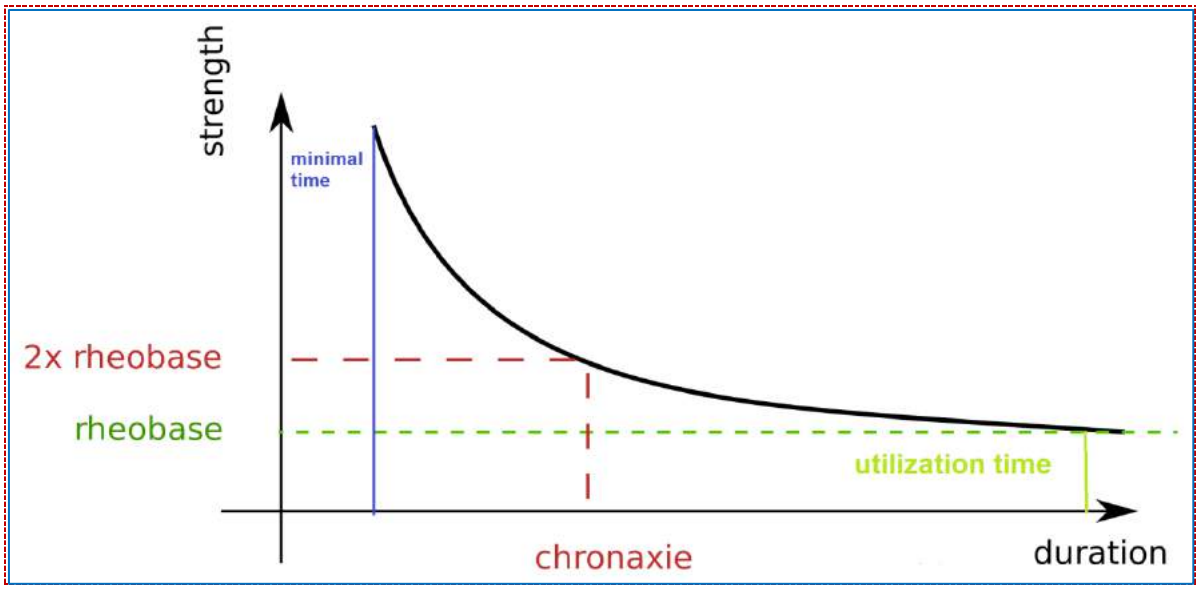
3. Rate of rise of intensity of the stimulus:

- If a subthreshold stimulus is applied to the nerve and increased **slowly**, the nerve **accommodate** itself to the passage of the current ⇨ **no** response.
- If intensity increased **rapidly**, accommodation is **not** observed ⇨ **response**.

Strength – Duration curve

Definition:

- It is a relationship between the **intensity** of the stimulus and the **time** of its application to the nerve to give a response.
- ***Within limits***, the stronger the stimulus, the shorter its duration.



Significance of the curve: →

1. **Rheobase:**
   - It is the minimal **strength** of galvanic current needed to give a response.
2. **Utilization time:**
   - It is the **time** required for intensity of rheobase to give a response.
3. **Minimal time:**
   - It is the **time** below which no excitation occurs whatever the strength of the stimulus.
4. **Chronaxie:**
   - **It is the time required for intensity of double rheobase to give a response.**
   - It is quantitative **measure** of tissue excitability.
   - The excitability is **inversely** proportional to the chronaxie.
   - The shorter the chronaxie, the greater the excitability.

CHANGES THAT ACCOMPANY NERVE EXCITATION

- The nerve excitation is associated by:
  (**Electrical** & **Excitability** & **Thermal** & **Metabolic**) changes.

[I] ELECTRICAL CHANGES IN NERVE

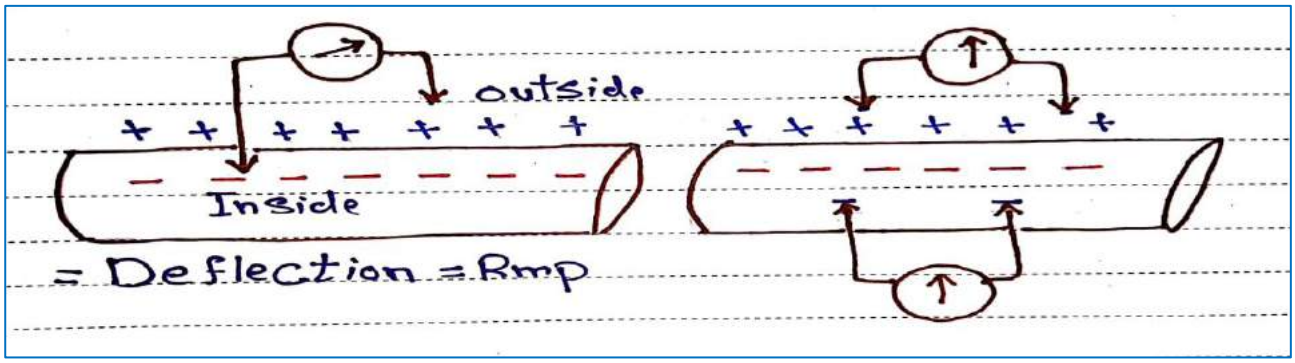
(A) resting membrane potential (RMP)

📖 Definition of RMP:

- It is the **P**otential difference between inside and outside the cell **M**embrane during **R**est, With inside relatively negative to outside.
- It ranges from -9 m.volt to -100 m.volt.
- In the nerve (-70 in medium sized nerve -90 in large nerve)
- In the muscle -90 m.volt In RBCs -30 m.volt.

📖 Evidence of RMP:

- If 2 electrodes are put bothon outer or on inner surface of cell membrane,
  → there is no potential difference.
- But, if one electrode is put on **outside** and the other **inside** the cell membrane, there is a potential difference.



📖 Causes of RMP:

- It is due to **UNEQUAL DISTRIBUTION of IONS** across the cell membrane.
- More cations outside & more anions inside.
- More **Na^+ outside** & More **K^+ inside**.

Extra-cellular		Intra-cellular	
Na^+	= **150** mEq/L. **Main Cation**	Na^+	= **15** mEq/L.
K^+	= **3 – 5** mEq/L.	K^+	= **150** mEq/L. **Main Cation**
Cl^-	= 100 mEq/L. **Main Anion**	$Protein^-$	= 40 mEq/L.
HCO_3^-	= 28 mEq/L.		

- This unequal distribution of ions is caused by **three factors in the MEMBRANE: (causes of RMP)**:
  1. **S**elective **P**ermeability.
  2. **S**odium **P**otassium **P**ump.
  3. Membrane is impermeable to the intracellular **P**rotein anions.

1. Selective permeability of the cell membrane:

➢ Cell membrane channels:

- The cell membrane has pores (channels) of two types:

A. Leakage channels: (passive) that are characterized by:

- They are opened **all time**, **not gated** → See before " cell transport "
- The Membrane is More **P**ermeable to **P**otassium (50 – 100 times) than to sodium.
- **Why** ? Because the hydrated K^+ is smaller in size than the hydrated Na^+
- So, **K^+ outflux is more than Na^+ influx**.

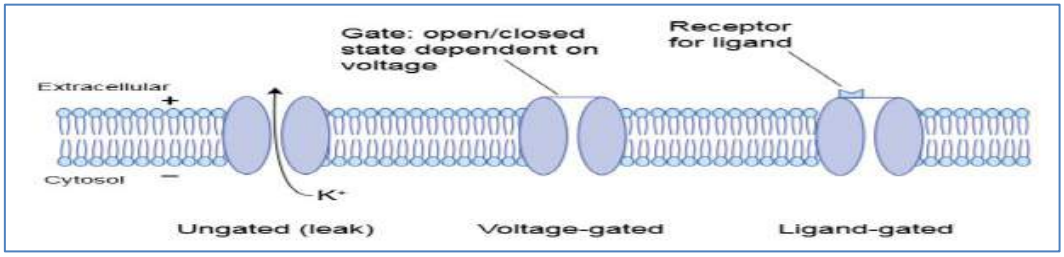
B. Gated channels: (active) that are characterized by:

- These gates may be opened or closed by 2 mechanisms:
  1) **Voltage gated channels:** open by change in membrane **voltage** (change in ionic composition).
     e.g. voltage gated Na^+ channel & voltage gated K^+ channel

	1. Voltage-gated Na^+ channels	2. Voltage-gated K^+ channels
Gates	Na^+ channel has **2 gates**: a) **O**uter gate (rapid or **A**ctivation gate). b) **In**ner gate (slow or **In**activation gate).	K^+ channel has a **one gate** Which is located inside the cell membrane. This gate is **very slow**.

  2) **Chemical gated channels (ligand channels):** open by **chemical** substances.
     e.g. Channels that open by Ach

During rest: the movement of ions is through **leakage** channels.
During stimulation and action potential: it occurs via **gated** channels.



Cell membrane permeability:

Nernest equation:

- Used to determine the equilibrium potential of **each ion**.
- Electromotive force (EMF) = $- 61 \log \frac{\text{conc.inside}}{\text{conc.outside}}$

As regard to Na^+	As regard to K^+
• At equilibrium: EMF = - 61 log (15/150) = **+ 61 m.volt**.	• At equilibrium: EMF = - 61 log (150/5) = **- 94 m.volt**.
RMP is near to the equilibrium potential of K^+ Indicating that **K^+ permeability** is the **main** force responsible for the RMP. → **MCQ**!!	

Goldman equation:

- It is used to determine the equilibrium potential of **all ions**, which is about **-86 m.volt** (near to the equilibrium potential of K^+) indicating that K^+ permeability is the main force responsible for the RMP.

2. Na^+ - K^+ ATPase pump:

➢ Site of Na^+ - K^+ pump:

- Cell membrane of any living cell.

➢ Na^+ - K^+ pump needs(requirements): mcq !!!

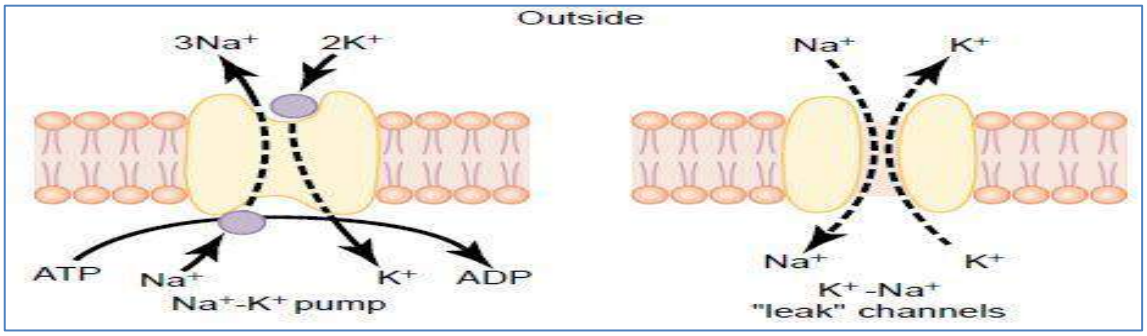
1) Large **carrier protein** in the cell wall:
   a) Its internal surface has 3 receptors for Na^+
   b) Its external surface has 2 receptors for K^+.
2) Energy source (**ATP**).
3) ATPase **enzyme** for liberation of energy.

➢ When activated:

- It is activated by energy from splitting of ATP by ATPase enzyme.
- **Na^+** is pumped to **outside** the cell against conc. & electrical gradient
- **K^+** is pumped to **inside** the cell against conc. gradient only.

➢ Na^+ - K^+ pump is:

- Inhibited by → Hypoxia & Oubain (Digitalis drug)



➢ **Importance of the Na^+ - K^+ pump: → MCQ**

1) Maintenance of **Na^+ (extra cellular)** and K^+ (intracellular).
2) Control of **cell volume**, as if Na^+ remains inside the cell, water enters by osmosis and the cell swells
3) It is **electrogenic** pump, as it maintains RMP more negative inside by **(-4 m.volt)**.

➢ **Differences between selective permeability and Na^+ - K^+ pump:**

Selective permeability	Na^+ - K^+ pump
Initiation of RMP by **-86** mV.	Maintenance of RMP by **-4** mV.
Passive process (simple diffusion). No energy needed.	**Active** process (1ry active transport). Energy needed.
K^+ is mainly responsible.	**Na^+ & K^+** are responsible.

3. Membrane is impermeable to the intracellular protein:

- The **membrane is impermeable to the intracellular protein anions** with large molecular weight ⇨ more negative charges inside the cell.

(B) Action potential & its ionic basis

📖 **Definition of action potential (AP):**

- It is a Transient change in the resting membrane potential as a result of application of Threshold stimulus.

📖 **Application of threshold stimulus to nerve fiber is followed by:**

1. Stimulus artifact:

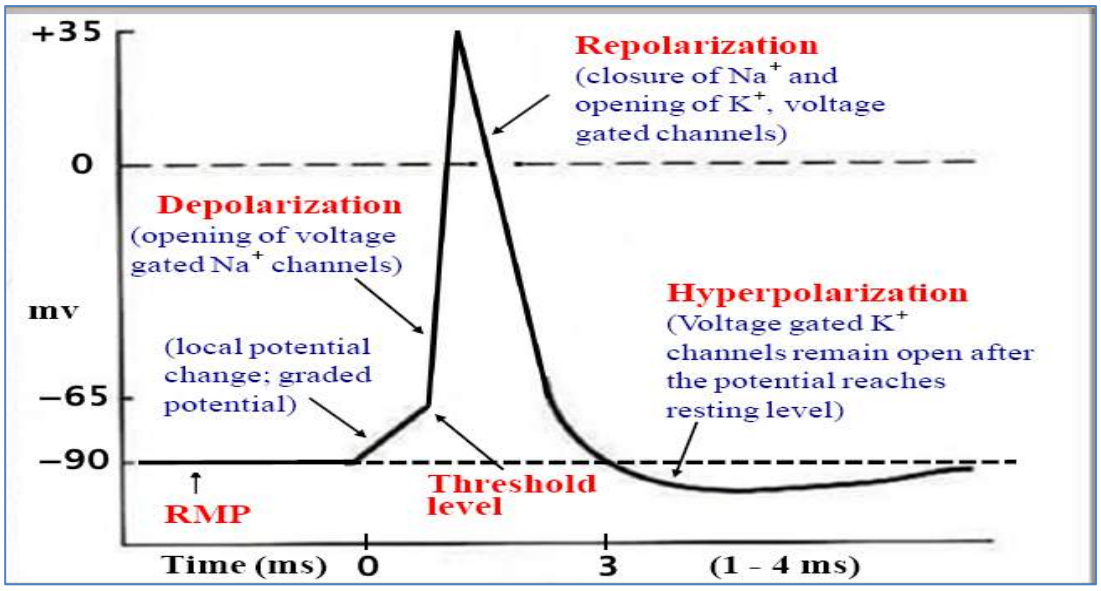
- Caused by application of stimulus → (indicates beginning of stimulus).

2. Latent period:

- It represents the time that the nerve impulse takes to travel from the stimulating electrode to the recording electrode.
- It is used to calculate speed of conduction in the axon.
- **Speed of conduction = distance between electrodes / latent period.**

3. Spike potential: (Depolarization and Repolarization):

A. Depolarization: (ascending limb):	B. Repolarization: (descending limb):
Cause of depolarization: Activation of voltage gated Na^+ channels ⇨ ⇧ **Na^+ influx.**	**Cause of repolarization:** a) Inactivation of voltage gated Na^+ channels ⇨ ⇩**Na^+ influx.** b) Activation of voltage gated K^+ channels ⇨ ⇧ **K^+ outflux.**
Depolarization occurs in 3 steps: **1) Slow depolarization:** - Depolarization of **25 mv**. - So, RMP is changed from -90 to -65 mv. **2) Rapid depolarization:** - From **-65** mv (**firing level**) till the potential zero mv. **3) Reversal of polarity (overshoot):** - From zero mv till **+35 mv**. - So, magnitude of the depolarization = **125 mv** (from -90 to +35).	**Repolarization occurs in 3 steps:** **1) Rapid repolarization:** - During which the membrane restores **70%** of its resting condition. - **Cause:** a) Inactivation of voltage gated Na^+ channels ⇨ ⇩**Na^+ influx.** b) Activation of voltage gated K^+ channels ⇨ ⇧ **K^+ outflux.** **2) After depolarization (Negative after potential):** - After 70% of repolarization, the rate of repolarization becomes slow. - **Cause:** - ⇩ **K^+ gradient ⇨ slow K^+ efflux ⇨ slow repolarization.** **3) After hyperpolarization (Positive after potential):** - After reaching RMP, there is overshoot of about **1-2 m.volt** So, membrane is hyperpolarized (**-92 mV**). - **Cause:** **Delayed closure of K^+ channels ⇨ more K^+ efflux.** **Then, the membrane returns to normal RMP.**



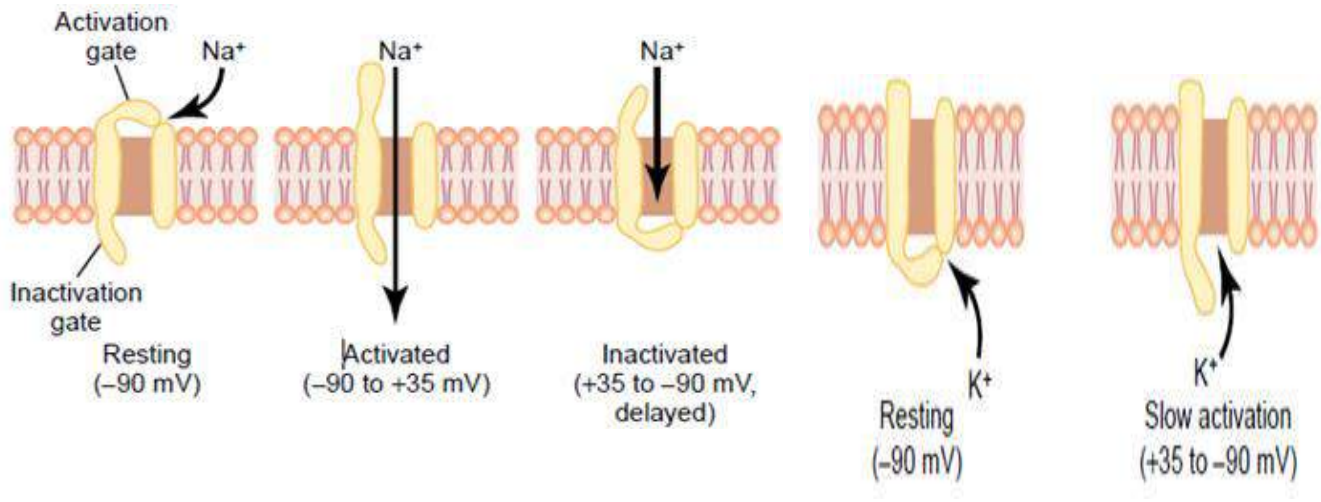
🕮 Ionic basis of action potential:

A. The ionic channels:

- The changes in the membrane potential during phases of action potential depend on the presence of the **voltage gated channels:**

1) Voltage-gated Na^+ channels **2) Voltage-gated K^+ channels**

	Voltage-gated Na^+ channels	Voltage-gated K^+ channels
During rest at RMP -90 m.volt	- **activation** gate is **closed** **inactivation** gate is **opened**. - So, no Na^+ influx.	- The gate is **closed**.
activation	- Change of membrane potential by 25 m.volt (from -90 to -65 m.volt) i.e. **firing level**. - The **activation** gate is **opened** and Na^+ (influx) reach maximum till the potential of +35 m.volt. - **At +35 m.volt, inactivation gate** is closed ⇨ no more Na^+ influx.	- Depolarization ⇨ **slow** opening of K^+ channel which **coincides** to closure of Na^+ gates ⇨ repolarization. - **Delayed** closure of K^+ channels ⇨ hyperpolarization.
Then, resting condition returns	- when the RMP returns to normal.	- when the RMP returns to normal.



B. The ionic changes during action potential:

(1) During depolarization phase:

- Opening of some outer Na^+ gates ⇨ Na^+ influx ⇨ more opening of gates and more depolarization (**+ve feedback**) till reaches firing level then depolarization occur rapidly till its peak (+35 mv).
- Then, **the inner Na^+ inactivation gates close.**

(2) During repolarization:

- It is caused by: a) Inactivation of voltage gated Na^+ channels ⇨ ⇩ Na^+ influx.
  b) Activation of voltage gated K^+ channels ⇨ ⇧ K^+ outflux.

(3) After depolarization (-ve after potential)l:

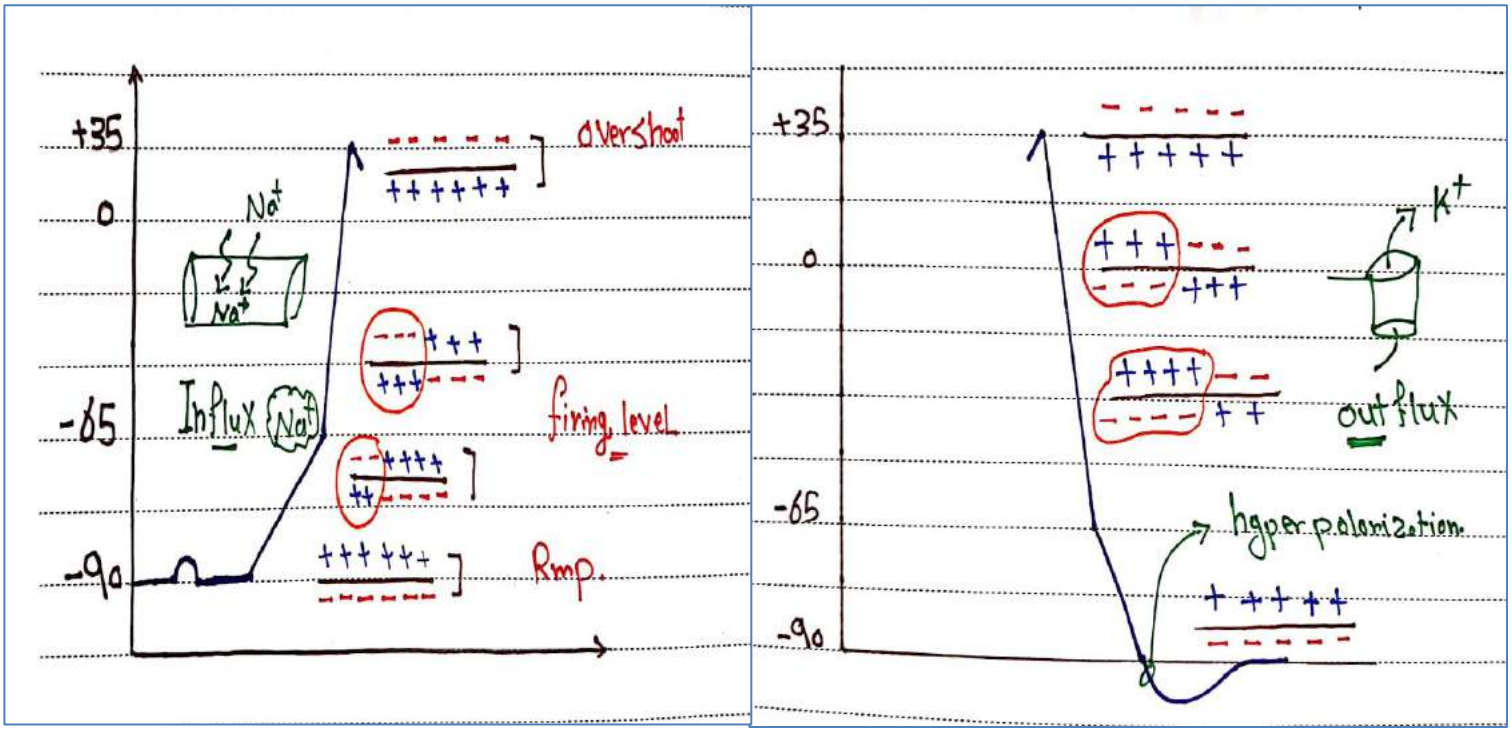
- Caused by: ⇩ K^+ gradient ⇨ slow K^+ efflux ⇨ slow repolarization.

(4) After hyperpolarization (+ve after potential):

- Caused by: Delayed closure of K^+ channels ⇨ more K^+ efflux.

C. Stimulation of the nerve is followed by: → MCQ

1) Opening of outer Na^+ gate ⇨ activation of Na^+ channel. (Depolarization).
2) Closure of inner Na^+ gate ⇨ inactivation of Na^+ channel.
3) Opening of K^+ gate ⇨ activation of K^+ channel. (Repolarization).



FACTORS AFFECTING EXCITABILITY OF NERVE

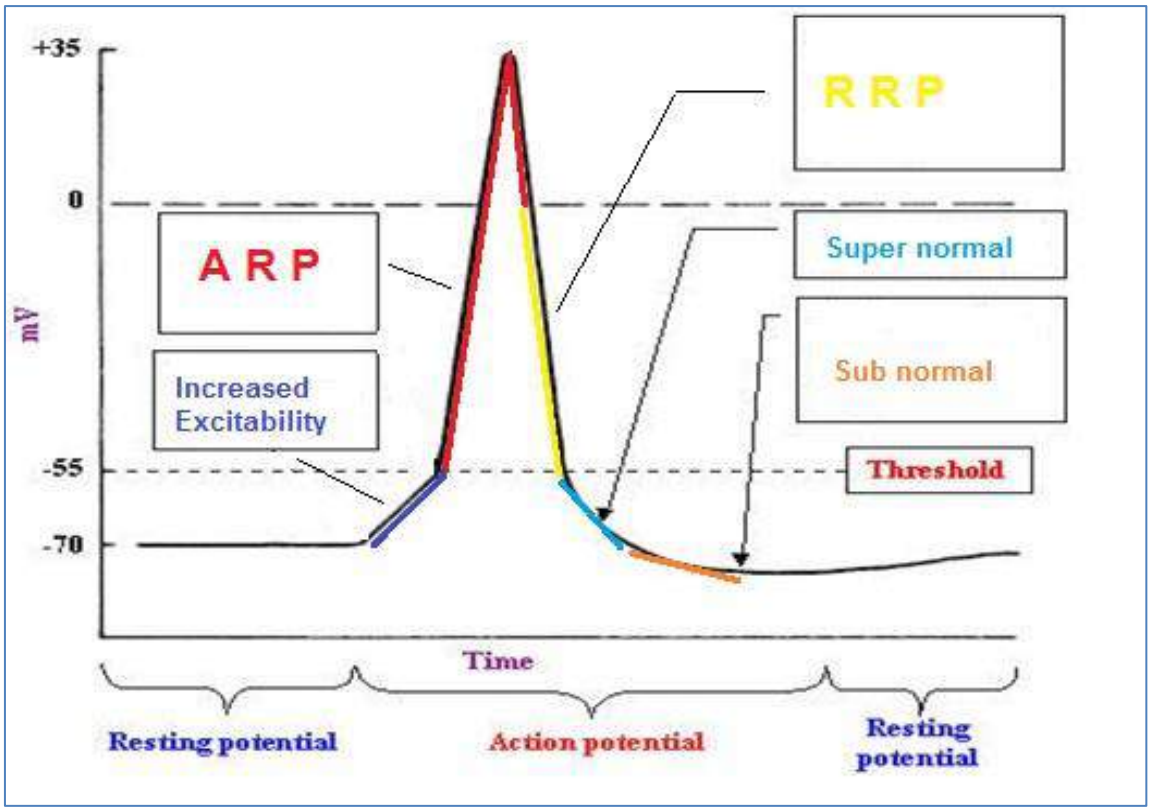
Factors increase excitability	Factors decrease excitability MEMBRANE STABILIZER NERVE BLOCK
Warming.	Cooling.
Alkalosis.	Acidosis.
⇧ **Na^+ permeability** by: a) ⇩ Ca^{++} conc. in extra cellular fluid (ECF). as in ***tetany***. b) Veratrine.	⇩ **Na^+ permeability** by: a) ⇧ Ca^{++} conc. in extra cellular fluid (ECF). b) Tetrodotoxin (block voltage Na^+channels). c) ***Local anesthesia*** as novocaine which cause paralysis of voltage gated N^+ channels.
⇧ **K^+ conc.** Extracellular: as it leads to ⇩ K^+ efflux and state of partial depolarization.	⇩ **K^+ conc.** Extracellular: as it leads to ⇧ K^+ efflux and state of hyperpolarization. as in ***familial periodic paralysis***.
	Mechanical pressure.
	Decrease blood supply to the nerve as in: a) Peripheral ischemia & hypoxia. b) ***Diabetes mellitus***.
Catelectrotonus.	Anelectrotonus.

- **Familial periodic paralysis:** hereditary disease ⇨ ⇩ extracellular K^+ ⇨ ⇩ excitability & contraction of the muscle ⇨ muscle relaxation.
- **Tetany:** ⇧ neuromuscular excitability due to ⇩ extracellular ionized Ca^{++}.

[II] EXCITABILITY CHANGES IN NERVE

- At first, there is increase in excitability till the **firing level**.
- Then, the following changes occur:

	Absolute Refractory Period (ARP)	Relative Refractory Period (RRP)	Supernormal Phase	Subnormal Phase
Definition	No response to any stimulus. (**loss** of excitability).	Stronger stimulus needed to give response (**low** excitability)	Weak stimulus may give response (**high** excitability)	Stronger stimulus needed to give response (**low** excitability).
Timing	Coincides with depolarization from **firing level till first 1/3 of repolarization**.	Coincides with the **lower part of repolarization**.	Coincides with **after depolarization**. (**-ve afterpotential**).	Coincides with **after hyperpolarization**. (**+ve after potential**).
Cause	Na^+ gates are **inactive** and not open again till return of membrane potential to the resting state.	a) **Some Na^+** gates are partially active. But, also b) **K^+ channels** are partially opened causing depolarization is difficult.	Membrane is partially **depolarized** ⇨ has low threshold for firing level ⇨ easy stimulation.	Membrane is **hyperpolarized** ⇨ has high threshold for firing level ⇨ difficult stimulation.



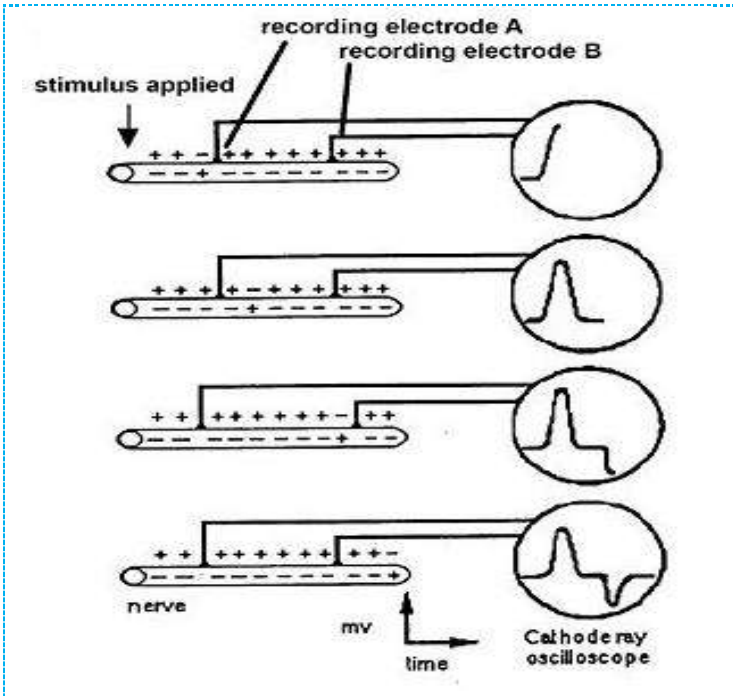
TYPES OF ACTION POTENTIAL

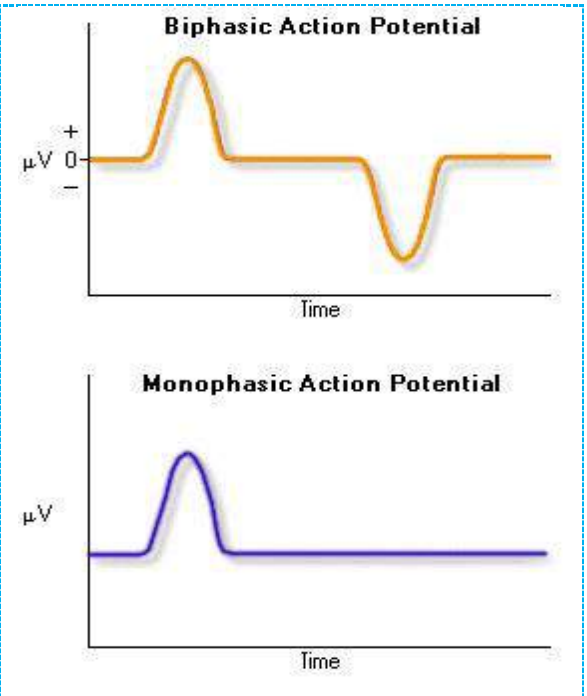
1. Biphasic action potential:

- It is the potential changes between 2 areas (A & B) both on the **outer surface** of the nerve fiber membrane.
- The stimulus is applied near the A point.
- It consists of the following phases:
  1) At first, both (A) & (B) are +ve
     So, no potential difference between A & B. (isoelectric).
  2) When depolarization wave reach (A) it becomes (-ve) relative to (B) (+ve)
     So, deflection is recorded.
  3) When the depolarization wave leaves (A) it repolarizes to (+ve).
     So, no potential difference between A & B. (isoelectric).
  4) When depolarization wave reach (B) it becomes (-ve) relative to (A) (+ve)
     So, deflection is recorded in the opposite direction.
  5) When the depolarization wave leaves (B) it repolarizes to (+ve).
     So, no potential difference between A & B. (isoelectric).

2. Monophasic action potential:

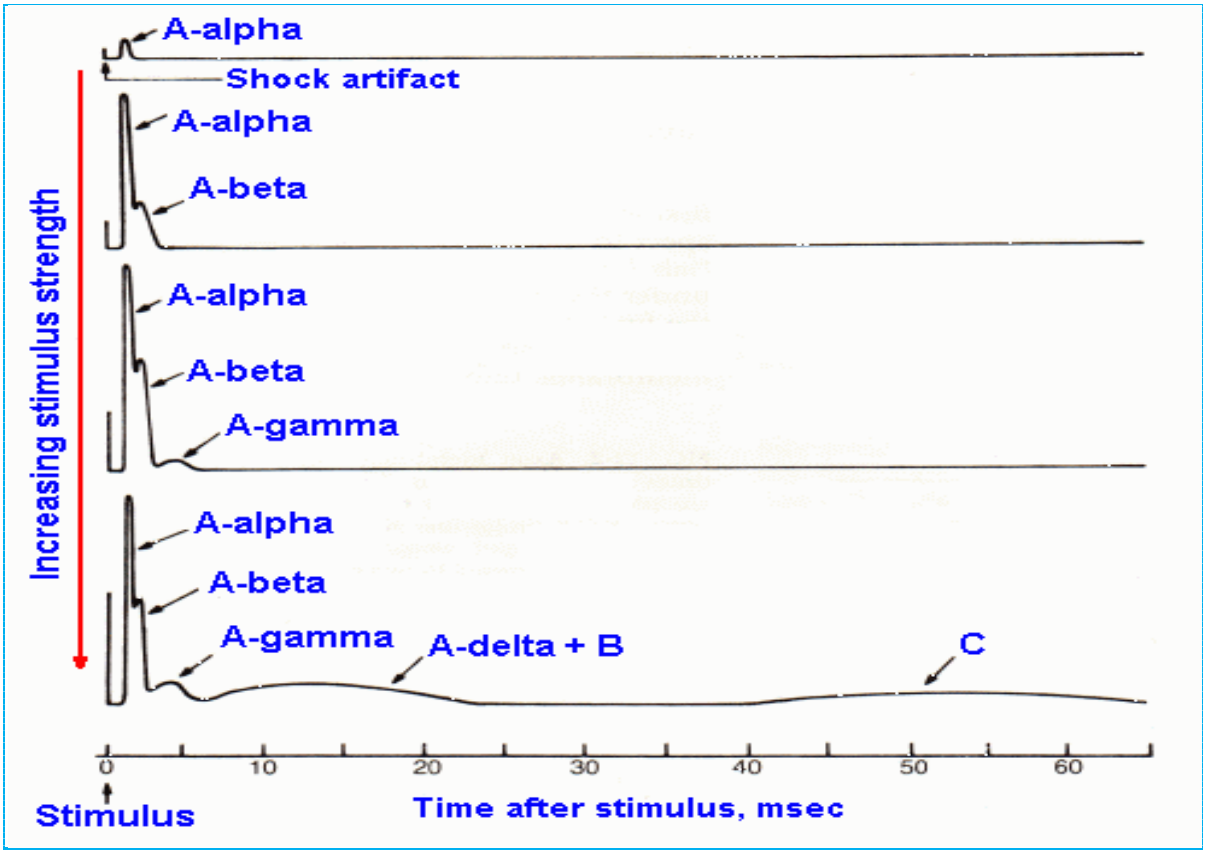
- It is the recording of potential difference between **inside and outside** the nerve fiber membrane (see before).
- Also it occurs in **Demarcation potential** in which the two electrodes are put on **outer surface** of membrane, but, membrane under one point is **damaged**.
  ⇨ So, the impulse at this damaged point is monophasic.





3. Compound action potential:

- As the **mixed nerve** consisted of many nerve fibers, these fibers have different diameters and excitability.
- So, stimulation of the mixed nerve depends on the intensity of stimulus and is called the compound action potential:
    1) **Subthreshold** stimulus ⇨ no response.
    2) **Threshold** stimulus ⇨ excitation of the most excitable fibers.
    3) **Suprathreshold** stimulus ⇨ more fibers are excited ⇨ more response.
    4) **Maximal** stimulus ⇨ all fibers are excited ⇨ maximal response.
    5) **Supramaximal** stimulus ⇨ the same as maximal response.



4. Graded (grated) potential (receptor potential):

- It is **local response**. (see later).
- It occurs in the **postsynaptic** neuron & Motor end plate (**MEP**) & **sensory receptors**.

Conduction of nerve impulse

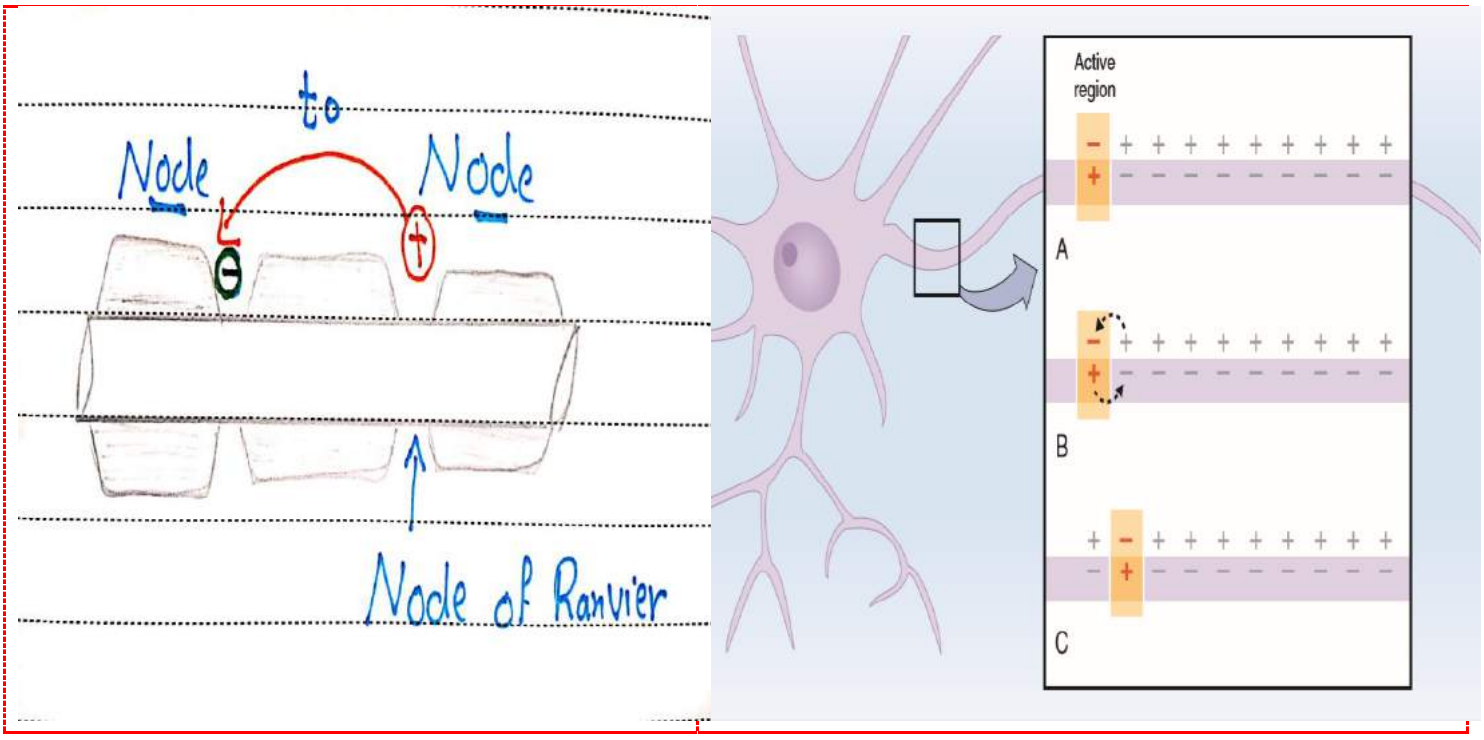
🕮 Definition:

- It is the transmission of excitation wave in the form of **depolarization** followed by **repolarization**.

🕮 Mechanisms:

1- In the unmyelinated nerve fibers:

- During rest, membrane is polarized. (+ve outside).
- At site of stimulation, the membrane is depolarized (-ve outside).
- So, a local current flow occurs between depolarized area and surroundings areas:
  - **In the inner surface:** +ve charges migrate from the point of depolarization to the surrounding sites.
  - **In the outer surface:** +ve charges migrate from the surrounding sites to point of depolarization.
- **The results are:**
  - **Point of stimulation** begins to repolarize.
  - **The surrounding sites** begin to depolarize partially till they reach the firing level ⇨ action potential.
- This is repeated. So, conduction occurs along the nerve fiber.
- It is called the (**Current sink**).
- Speed of propagation is directly proportional to the diameter of the nerve fiber.



2- In the myelinated nerve fibers:

- The same mechanism as in the unmyelinated. But, the impulse jump from one node of Ranvier to the other because the myelin is insulator for current.
- So, it is called (**Jumping** or **Saltatory** or **Node to node**) conduction.
- **It is characterized by:**
  1) The rate of conduction in the myelinated nerve is **50 to 100 times faster** than in the unmyelinated.
  2) It occurs with less energy for Na-K pump (**more economic**).
  3) It has **R**apid **R**epolarization.

🕮 Calculation of speed of conduction:

- Speed of conduction = distance between electrodes / latent period.
-

🕮 Factors affecting conductivity in the nerve:

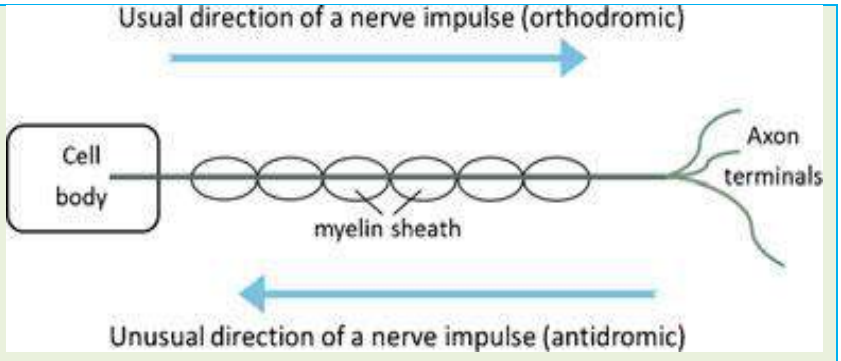
1. **Diameter of the nerve fiber:**
   - ⇧ Diameter ⇨ ⇧ speed of conduction.
   - Nerve fibers are classified into 3 types according to diameter:

	A Fibers	B Fibers	C Fibers
Diameter	**1 – 20 μ** Subtypes (α, β, γ, δ).	**1– 5 μ**	**Less than 1 μ**
Speed	**20 – 120 m/sec**	**5 – 15 m/sec**	**0.5 – 2 m/sec**
Duration of AP	0.5 msec.	1 msec.	2 msec.
Susceptible to	Mechanical pressure.	Hypoxia.	Local anesthesia.
Myelin sheath	Myelinated.	Myelinated.	Non-myelinated.
e.g.	Somatic nerve fibers.	Preganglionic.	Post ganglionic.

2. **Myelination:** myelinated nerve is 50 to 100 times faster than unmyelinated.
3. **Mechanical pressure:** ⇨ ⇩ conduction (more effect on A - fibers).
4. **Hypoxia:** ⇨ ⇩ conduction (more effect on B - fibers).
5. **Local anesthetics:** ⇨ ⇩ conduction (more effect on C - fibers).

Direction of conduction:

1) **Ortho-dromic conduction:** in one direction from cell body along the axon till its end then to other neuron.
2) **Anti-dromic conduction:** conduction in opposite direction of the normal pathway.

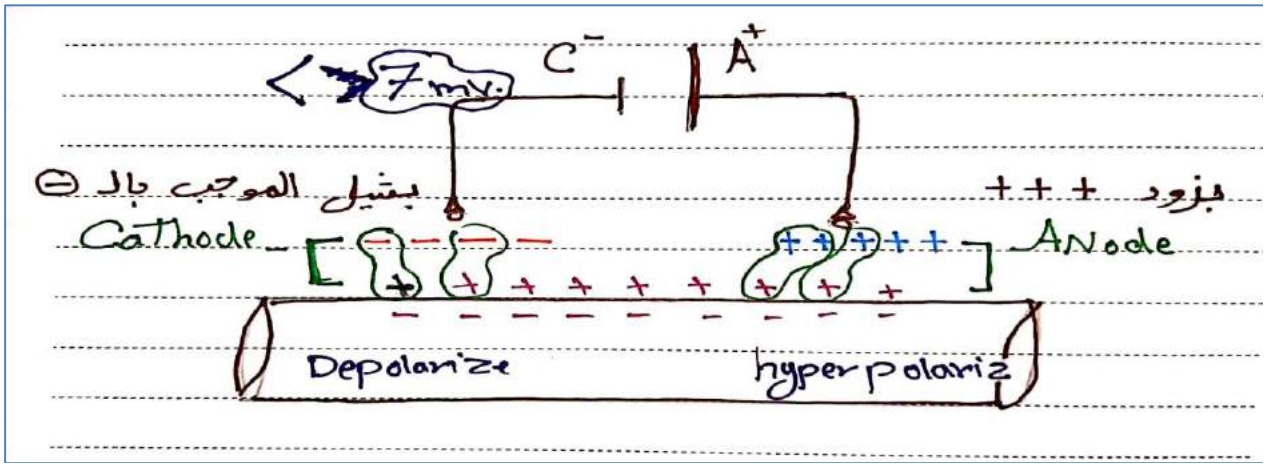

Usual direction of a nerve impulse (orthodromic)
Cell body
Axon terminals
myelin sheath
Unusual direction of a nerve impulse (antidromic)

Effects of sub threshold stimulus

1. Electrotonus:

- It is the localized potential changes that occur in nerve during its stimulation by **subthreshold constant** stimulus.
- This stimulus is obtained from a **battery** and either the cathode (-ve) or anode (+ve) electrode can be used to stimulate the nerve.
- The localized potential changes that occur by the cathodal end is called catelectrotonus & The localized potential changes that occur by the anodal end is called anelectrotonus.

	Cat-electrotonus	An-electrotonus
Definition	Localized partial **depolarization** Caused by **Passive** addition of **–ve** charges at the **outer** membrane surface.	Localized **hyperpolarization** Caused by **Passive** addition of **+ve** charges at the **outer** membrane surface.
Excitability	Increased.	Decreased.
Chronaxie	Short.	Long.
Effect of ⇧ Stimulation	Local response.	Anodal block.



2. Local response (local excitatory state):

- At the cathode, if the intensity of stimulus increases ⇨ depolarization increases **passively** and **partially active** by opening of some Na^+ channels to produce 7 - 25 mV depolarization ⇨ local response.
- But, the opened gates are not enough to produce action potential because the nerve doesn't reach the firing level.
- Also, K^+ efflux prevents the action potential to occur.

Local response	Action potential
Caused by **Subthreshold** stimulus.	**C**aused by **threshold** stimulus.
Localized.	**C**onducted (propagates) in both directions.
Longer duration.	**C**onstant duration.
Not obey **A**ll or none law ⇨ can be graded.	Obeys **A**ll or none law ⇨ **can't** be graded (constant amplitude).
No ARP. ⇨ can be summated.	Has **A**RP ⇨ **can't** be summated.
Excitability increased.	Variable (4 phases of excitability changes).
Depolarization (EPSP) or hyperpolarization (IPSP).	**Always cause depolarization.**

📖 Stimulation by cathode resulted in three types of depolarization:

	Catelectrotonus	Local response	Firing level (AP)
Stimulus	Subthreshold.	Subthreshold.	Threshold or Supra.
Depolarization	Less than **7 mv**.	From **7 to 25**.	**25 or more**.
Mechanism	Passive.	Passive & partially active.	Active.
Effect	Repolarization mask this effect.	Repolarization mask this effect.	Depolarization force is more & AP resulted.

[III] METABOLIC CHANGES IN NERVE

- **Energy is needed for:**
  1) Na^+-K^+ pump to maintain RMP.
  2) Conduction of the nerve impulse.
- **Source of energy:** Glycogen $\xrightarrow[\text{oxidation}]{\text{anerobic}}$ lactic acid + ATP.
- **Vitamin B12:** is required for **M**etabolism & **M**yelination.

[IV] THERMAL CHANGES IN NERVE

1) **Resting heat:** little heat due to low metabolic rate.
2) **Initial heat:** due to breakdown of ATP for action potential.
3) **Recovery heat:** after action potential, **30 times** as initial heat. Required for re-synthesis of ATP by aerobic reactions.